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(54) Title: NOVEL MEDICAMENT (57) Abstract The present invention relates to novel medicaments containing GLP-1(7-37), GLP-1(7-36)amide or analogues or derivatives thereof and a phospholipid. The medicaments which are suited for nasal administration have a very favourable absorption profile.		

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NOVEL MEDICAMENT

FIELD OF THE INVENTION

The present invention relates to novel medicaments containing GLP-1(7-37), GLP-1(7-36)amide or analogues or functional derivatives thereof and a phospholipid, and to a method for preparing such medicaments.

BACKGROUND OF THE INVENTION

Glucagon-like peptide-1, also referred to as GLP-1, is a peptide sequence found in the C-terminal portion of mammalian proglucagon. Prior to 1985, no definite biological activity of GLP-1 had been reported. However, in 1985 it was demonstrated that GLP-1(1-36)amide, like glucagon, stimulates insulin release from isolated precultured rat pancreatic islets in the presence of glucose in a dose-dependent manner (Schmidt, W.E. et al. Diabetologia 28 (1985) 704-7). This finding suggests that GLP-1(1-36)amide and related peptides might be useful in the treatment of type 2 diabetes. Due to its substantially closer sequence homology to glucagon and glucose dependent insulintropic peptide, also referred to as GIP, Schmidt et al. suggested that an even stronger glucagon- and/or GIP-like biological activity could be expected with GLP-1(7-36) than with the intact peptide. In recent years, particular interest has focused on the GLP-1 fragments GLP-1(7-37) and GLP-1(7-36)amide and analogues and functional derivatives thereof. The amino acid sequence of GLP-1(7-36)amide and GLP-1(7-37) is given in formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-
Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-
Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X

(I)

which shows GLP-1(7-36)amide when X is NH₂ and GLP-1(7-37) when X is Gly-OH.

Thus, International Patent Application No. WO 87/06941 (to The General Hospital Corporation) relates to a peptide fragment which comprises GLP-1(7-37) and functional derivatives thereof and to its use as an insulintropic agent.

International Patent Application No. 90/11296 (to The General Hospital Corporation) relates to a peptide fragment which comprises GLP-1(7-36) and functional derivatives thereof and has an insulintropic activity which exceeds the insulintropic activity of GLP-1(1-36) or GLP-1(1-37) and to its use as an insulintropic agent.

International Patent Application No. 91/11457 (to Buckley et al.) relates to effective analogues of the active GLP-1 peptides 7-34, 7-35, 7-36, and 7-37.

SUMMARY OF THE INVENTION

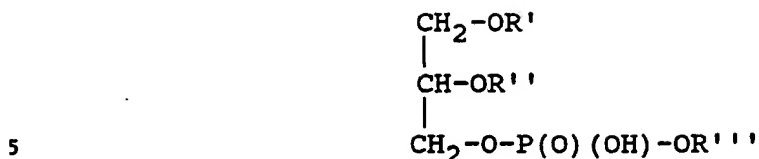
The present invention is based on the fact that when GLP-1 related peptides are administered in a formulation comprising certain phospholipids, a very favourable absorption profile is found. Also, the phospholipids exert a stabilizing effect on the peptides.

Thus, in its broadest aspect the present invention relates to a medicament for intranasal administration of a peptide fragment of formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X

(I)

wherein X is NH₂ or Gly-OH, or analogues or functional derivatives thereof, which medicament further comprises at least one phospholipid of the general formula II:



(II)

wherein R' and R'' are the same or different each representing hydrogen, alkyl, alkenyl, alkanoyl, alkenoyl, alka-
 10 dienoyl, alkatrienoyl or alkatetraenoyl containing not more than 14 carbon atoms in each group, with the proviso that R' and R'' are not hydrogen at the same time, and R''' is 2-(trimethylammonio)ethyl, 2-aminoethyl or 2,3-dihydroxypropyl, to a method of making such a medicament, and to the use of such a medicament as an insulinotropic agent in the
 15 treatment of diabetes.

In a first preferred embodiment, the invention relates to a medicament comprising GLP-1(7-36)amide.

In a further preferred embodiment, the invention relates to a medicament comprising GLP-1(7-37).

20 In a further preferred embodiment, the invention relates to a medicament comprising fragments of GLP-1(7-37).

In a further preferred embodiment, the invention relates to a medicament comprising functional derivatives of fragments of GLP-1(7-37).

25 In a further preferred embodiment, the invention relates to a medicament comprising analogues of GLP-1(7-37).

In a further preferred embodiment, the invention relates to a medicament comprising functional derivatives of analogues of GLP-1(7-37).

30 In a further preferred embodiment, the invention relates to a medicament comprising a phospholipid of formula II wherein R''' is 2-(trimethylammonio)ethyl.

In a further preferred embodiment, the invention relates to a medicament comprising a phospholipid of formula
 35 II wherein R' is alkyl having from 4 to 12 carbon atoms.

In a further preferred embodiment, the invention relates to a medicament comprising a phospholipid of formula II wherein R' is alkanoyl having from 4 to 12 carbon atoms.

In a further preferred embodiment, the invention
5 relates to a medicament comprising a phospholipid of formula II wherein R' is decanoyl.

In a further preferred embodiment, the invention relates to a medicament comprising a phospholipid of formula II wherein R' is hydrogen, with the proviso that R'' is
10 different from hydrogen.

In a further preferred embodiment, the invention relates to a medicament comprising a phospholipid of formula II wherein R'' is alkyl having from 4 to 12 carbon atoms.

In a further preferred embodiment, the invention
15 relates to a medicament comprising a phospholipid of formula II wherein R'' is alkanoyl having from 4 to 12 carbon atoms.

In a further preferred embodiment, the invention relates to a medicament comprising a phospholipid of formula II wherein R'' is decanoyl.

20 In a further preferred embodiment, the invention relates to a medicament comprising a phospholipid of formula II wherein R'' is hydrogen, with the proviso that R' is different from hydrogen.

In a further preferred embodiment, the invention
25 relates to a medicament comprising didecanoyl L- α -phosphatidylcholine.

In a further preferred embodiment, the invention relates to a medicament comprising a solid diluent.

In a further preferred embodiment, the invention
30 relates to a solid medicament comprising from 0.01 to 75 % (W/W), preferably from 0.1 to 50 % (W/W), more preferred from 0.5 to 25 % (W/W) of a peptide of formula I or analogues or functional derivatives thereof.

In a further preferred embodiment, the invention
35 relates to a solid medicament comprising from 10 to 99 % (W/W), preferably from 10 to 80 % (W/W), more preferred from 25 to 60 % (W/W) of a phospholipid of formula II.

In a further preferred embodiment, the invention relates to a medicament comprising a liquid diluent.

In a further preferred embodiment, the invention relates to a liquid medicament comprising from 0.0005 to 10 % (W/W), preferably from 0.001 to 5 % (W/W), more preferred from 0.01 to 5 % (W/W) of a peptide of formula I or analogues or functional derivatives thereof.

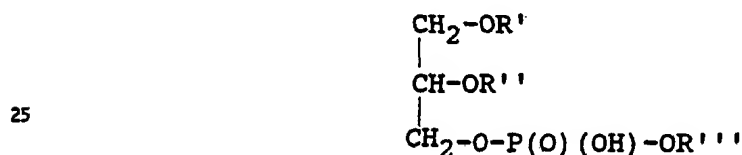
In a further preferred embodiment, the invention relates to a liquid medicament comprising from 0.01 to 20 % (W/W), preferably from 0.05 to 10 % (W/W), more preferred from 0.1 to 5 % (W/W) of a phospholipid of formula II.

In a further preferred embodiment, the invention relates to a method of making a medicament for intranasal administration of a peptide fragment of formula I:

15 His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X

(I)

wherein X is NH_2 or Gly-OH, and analogues and functional derivatives thereof and further comprising at least one phospholipid of the general formula II:



(II)

wherein R' and R'' are the same or different each representing hydrogen, alkyl, alkenyl, alkanoyl, alkenoyl, alka-
dienoyl, alkatrienoyl or alkatetraenoyl containing not more
than 14 carbon atoms in each group, with the proviso that R' and R'' are not hydrogen at the same time, and R''' is 2-

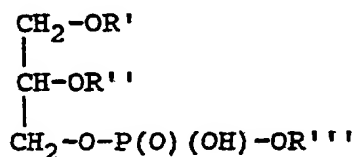
(trimethylammonio)ethyl, 2-aminoethyl or 2,3-dihydroxypropyl, which method comprises mixing the required amounts of the peptide fragment of formula I and at least one phospholipid of formula II, optionally in a solid or in a liquid diluent, and optionally further adding pH buffering agents, osmotic pressure controlling agents, preservatives or other ancillary agents.

In a further preferred embodiment, the invention relates to a medicament for intranasal administration of a peptide fragment of formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-
Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-
Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X

(I)

wherein X is NH_2 or Gly-OH, or analogues or functional derivatives thereof, characterized in that it further comprises at least one phospholipid of the general formula II:



(II)

wherein R' and R'' are the same or different each representing hydrogen, alkyl, alkenyl, alkanoyl, alkenoyl, alkatdienoyl, alkatrienoyl or alkatetraenoyl containing not more than 14 carbon atoms in each group, with the proviso that R' and R'' are not hydrogen at the same time, and R''' is 2-(trimethylammonio)ethyl, 2-aminoethyl or 2,3-dihydroxypropyl when used as an insuliontropic agent in the treatment of diabetes.

Functional derivatives of the peptides mentioned in this specification is to be construed as pharmaceutically acceptable lower alkyl esters formed with the C-terminal carboxylic acid group, alkyl meaning e.g. methyl, ethyl, 5 propyl, isopropyl, butyl, or tert-butyl or the amide, alkylamide or dialkylamide wherein alkyl is as mentioned above.

In this specification, analogues of GLP-1(7-37) means peptides which differ from GLP-1(7-37) in that at least one of the amino acid residues of GLP-1(7-37) independently have been exchanged by another amino acid residue, preferably one which can be coded for by the genetic code. The definition also comprises the case when amino acid residues are added at or deleted from the N-terminal and/or the C-terminal end of the peptide. Preferably, the total number 15 of such additions, deletions and exchanges does not exceed five, more preferred it does not exceed three.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above the formulations according to the present invention have a very favourable absorption profile. 20

One advantage is that the absorption is slightly protracted. This is expedient because administration of the medicament can then take place as required immediately before a meal. In this way the peptide becomes available 25 with its influence on the insulin secretion at the same time as the food arrives in the stomach. The patients need not plan their meals long time ahead and they thus experience an improved quality of life.

Another advantage with the formulations 30 according to the present invention is that they can provide a plasma concentration of the peptide which is fairly constant for a period of time sufficient to cover the duration of a meal. In contrast to this, as demonstrated in Example 2, formulations with tauro-24,25-dihydrofusidate, with α -

cyclodextrin or with a plain phosphate buffer having a pH value of 7.4 tend to give a course of the plasma concentration of the peptide which is less favourable: a very high initial peak which rather soon drops below the level obtainable with the formulations with phospholipids.

Examples of preferred compounds of formula II are:

dioctanoyl-L- α -phosphatidylcholine,
dioctyl-O-L- α -phosphatidylcholine,
10 didecanoyl-L- α -phosphatidylcholine,
didecyl-O-L- α -phosphatidylcholine,
decyl-O-L- α -lysophatidylcholine,
dilauroyl-L- α -phosphatidylcholine,
lauroyl-L- α -lysophosphatidylcholine.

15 The preparation of a number of compounds of formula II has been described, e.g. by E.C. Robles and D. Van Den Berg: Biochim.Biophys.Acta 187 (1969), 520 - 526, H.K. Mangold and F. Paltauf (Eds.) in: Ether Lipids, Chapter 3, Acad.Press 1983. Other compounds of formula II can be prepared by analogous methods.

The formulation of this invention may be liquid, e.g. adapted for administration as a spray or solid, e.g. a powder acceptable for snuffing. Liquid formulations, such as those based on aqueous formulations, may include ancillary agents, for example a pH-buffering system, preferably a phosphate, citrate or acetate buffer, a preservative and an osmotic pressure controlling agent, e.g. glycerol or sodium chloride. Powder formulations may contain the pharmaceutically active agent and the phospholipid of formula II in admixture with nasally acceptable powdery diluents or mixtures thereof, e.g. cellulose or derivatives thereof, for example cellulose ethers or sodium carboxymethylcellulose, starch, a long chain fatty acid or a salt thereof, e.g. aluminum stearate, an organic polymer, e.g. of an acrylic acid derivative or inorganic vehicles, such as talc or diatomaceous earth. Supplementary addition of water-absorbing poly-

mers, for example polyethylene glycol or polyvinyl pyrrolidone may be desirable to improve adhesion of the powder formulation to the nasal mucosa.

Preferred liquid formulations are those in which the diluent is water. Such formulations may be prepared by dispersing the phospholipid in the aqueous medium containing the GLP-1 derived active agent and ancillary agents, the dispersion being conducted by any method usually employed for suspension or emulsification, e.g. ultrasonic treatment. Adjustment of the aqueous phase to neutrality (i.e. to pH in the range from about 6.5 to about 8) may be accomplished in any of the preparatory steps.

Due to the fact that proteases and peptidases are associated with the nasal mucosa (see R.E. Stratford and V.H.L. Lee: Int.Journ.Pharmaceutics 30 (1986), 73 - 82) it may be desirable to incorporate biocompatible protease and peptidase inhibitors into polypeptide containing formulations.

The concentration to be used of the GLP-1 derived active agent in the formulations of this invention will of course depend on the particular agent chosen, on its efficacy, on a comparison of its bioavailability by nasal administration and by other routes of administration, for example injection or infusion, and on the desired frequency of administration. Such pharmacological data can routinely be obtained by in vivo studies designed by those skilled in the art.

The total daily dose of the GLP-1 derived active agent to be given which i.a. depends on the particular agent and on the condition of the patient is determined by a medically skilled person. The total daily dose is conveniently administered in submultiples thereof.

Generally, the total daily dose of a GLP-1 derived active agent to be administered nasally in the treatment of diabetes will be in the interval from 0.05 to 20 μ g per kilogram of body weight.

An exemplary mode of preparing a GLP-1(7-36) amide formulation of this invention wherein the diluent is water comprises dissolving GLP-1(7-36)amide in water optionally in the presence of an acid, for example hydrochloric acid. An aqueous solution of a preservative, for example phenol, an alkyl phenol, such as cresol, or methyl p-hydroxybenzoate, is prepared separately, optionally also containing an agent rendering the solution isotonic, such as sodium chloride or glycerol. Furthermore, the preservative solution may contain a buffering agent, such as sodium phosphate, sodium citrate, sodium acetate or TRIS (tris(hydroxymethyl)aminomethane) and a protease inhibitor. The resulting preservative solution is then admixed with the solution of GLP-1(7-36)amide, optionally followed by addition of a base, for example a sodium hydroxide solution, to adjust the pH value to neutrality. The phospholipid of formula II may be added to the solution of GLP-1(7-36)amide as a solution or an emulsion which is prepared by dissolving or suspending the phospholipid of formula II in water and, if necessary, subjecting any suspension to an ultrasonic treatment before mixing with the GLP-1(7-36)amide solution. Alternatively, the phospholipid solution or emulsion may, if desired, contain the buffering agent and preservative. After mixing, the pH value of the formulation may be readjusted to neutrality. Finally, the resulting solution is made up to the calculated volume by addition of water.

The formulations of this invention may be used in any dosage dispensing device adapted for intranasal administration. The device should be constructed with a view to ascertaining optimum metering accuracy and compatibility of its constructive elements, such as container, valve and actuator with the nasal formulation and could be based on a mechanical pump system, e.g. that of a metered-dose nebulizer, or on a pressurized aerosol system. The aerosol system requires the propellant to be inert towards the formulation. Suitable propellants may be selected among such gases as fluorocarbons, hydrocarbons, nitrogen and dinitrogen oxide

or mixtures thereof.

Some details concerning the use of GLP-1 related peptides in the treatment of diabetes can be found in our copending Danish patent application No. DK 0363/92 which was
5 filed simultaneously with the present application. The contents of said application is hereby incorporated in its entirety by reference.

The features disclosed in the present description, examples and claims may, both separately and in any
10 combination thereof, be material for realizing this invention in diverse forms thereof. The invention is further illustrated by the following examples which are not to be construed as limiting but merely as an illustration of some preferred features of the invention.

15 EXAMPLES

General methods

GLP-1(7-36)amide and GLP-1(7-37) were obtained from Bachem
Feinkemicalien AG (Switzerland) and Peninsula Laboratories
(England), respectively. The concentration of GLP-1(7-
20 36)amide and GLP-1(7-37) in solution was monitored by standard reversed phase HPLC employing a gradient of acetonitrile and 0.1% trifluoroacetic acid (10-100% over 30 minutes) with UV detection at 280 nm.

The concentration in plasma of GLP-1(7-36)amide and GLP-1(7-
25 37) was assayed by radioimmunoassay (RIA), essentially as described by Ørskov et al. (Scand. J. Clin. Lab. Invest. 47 (1987) 165-174). Antibodies were obtained as a generous gift from Dr. Jens J. Holst (The State University Hospital of Copenhagen).

Preparati n f nasal formulations

Phospholipid vehicle

2 g of didecanoyl L- α -phosphatidylcholine was mixed with 0.4 g of coconut oil, 0.2 g of cholesterol and 1.6 g of glycerol. To this mixture was added 5 mM sodium phosphate buffer having a pH value of 7.4 to a final volume of 100 ml and the resulting mixture was emulsified by ultrasonic treatment. The peptide in question was dissolved in this vehicle.

10 Tauro-24,25-dihydrofusidate vehicle

1 g of sodium tauro-24,25-dihydrofusidate was dissolved in 0.02 M sodium phosphate buffer having a pH value of 7.4 to a final volume of 100 ml. The peptide in question was dissolved in this solution.

15 α -cyclodextrin vehicle

The α -cyclodextrin was dissolved in distilled water, the peptide in question was added and the solution was freeze dried.

EXAMPLE 1

20 Stability of GLP-1(7-36)amide in solution.

A solution containing 0.5 mg/ml of GLP-1(7-36)amide in the above described phospholipid vehicle and a solution containing 0.5 mg/ml of GLP-1(7-36)amide in a 5 mM sodium phosphate buffer having a pH value of 7.4 were prepared.

25 The solutions were incubated at 4°C. At the times indicated in Table 1 samples were withdrawn and the content of intact GLP-1(7-36)amide was assayed by HPLC as described above. Table 1 shows the percentage of the initial amount of GLP-1(7-36)amide remaining in the phosphate buffer and in the phospholipid emulsion, respectively, at the times indicated.
30

Table 1

Time	Phosphate buffer	Phospholipid emulsion
Day 0	100	100
Day 7	49	97
Day 11	32	89
Day 25	11	85
Day 32	4	86

These data clearly demonstrate that the phospholipid vehicle strongly enhances the stability of GLP-1(7-36)amide in solution.

EXAMPLE 2

Pharmacokinetics of GLP-1(7-36)amide and GLP-1(7-37) in various nasal formulations

The study was carried out in fasted New Zealand White rabbits (male, 18-36 months old, weighing 3-4 kg) having an intravenous line in one ear for withdrawal of blood samples.

The following formulations were used in the study:

Formulation 1: GLP-1(7-36)amide (250 μ g) was dissolved in 1 ml of the phospholipid vehicle. 100 μ l of this liquid formulation was applied in each of the nostrils of the rabbits in which it was tested.

Formulation 2: GLP-1(7-37) (250 μ g) was dissolved in 1 ml of the phospholipid vehicle. 100 μ l of this liquid formulation was applied in each of the nostrils of the rabbits in

which it was tested.

5 Formulation 3: GLP-1(7-36)amide (50 μ g) was dissolved in 1 ml of the tauro-24,25-dihydrofusidate vehicle. 100 μ l of this liquid formulation was applied in each of the nostrils of the rabbits in which it was tested.

10 Formulation 4: GLP-1(7-36)amide (50 μ g) was mixed with 100 mg of α -cyclodextrin. 20 mg of this powder formulation was applied in one nostril of each of the rabbits in which it was tested.

15 Formulation 5: GLP-1(7-36)amide (50 μ g) was dissolved in 1 ml of a 20 mM sodium phosphate buffer having a pH value of 7.4. 100 μ l of this liquid formulation was applied in each of the nostrils of the rabbits in which it was tested.

20 The liquid formulations were administered using an Eppendorf multipipette while the powder formulation was administered by cautiously blowing 20 mg thereof from a small tube into one nostril. 1,5 ml blood samples were withdrawn at the times indicated in Table 2 and the plasma concentration of the GLP-1 (7-36)amide and GLP-1(7-37) respectively was assayed by RIA as indicated under General methods.

25 Table 2 shows the observed increments in the plasma concentrations of GLP-1(7-36)amide and GLP-1(7-37) respectively as a function of time after administration of the formulations 1 to 5 at 0 minutes. The plasma concentrations are corrected for the basal level of GLP-1(7-36)amide or GLP-1(7-37) respectively found in the plasma at 0 min and are expressed as percentage of the maximal plasma concentrations observed.
30 The maximal plasma concentrations observed for formulations

1 to 5 were 248 pM, 377 pM, 124 pM, 143 pM and 36 pM, respectively.

Table 2

Minutes after administration	Formulation No.				
	1	2	3	4	5
0	0	0	0	0	0
2	0	28	62	97	17
4	17	29	100	100	100
6	41	69	93	73	92
8	62	82	79	52	94
10	78	96	87	41	64
12	96	100	69	25	56
14	100	94	56	18	39
16	95	51	37	10	28
18	100	-	40	12	42
20	79	-	29	3	28
25	59	64	37	2	0
30	38	47	17	5	0

These data clearly demonstrate that only the phospholipid formulations (formulations 1 and 2) provide a protracted delivery of the peptide. Furthermore, the plasma concentrations show a plateau (with plasma concentrations > 50% of the maximal concentration) between 6 and 25 minutes after the delivery, exclusively when the phospholipid formulation is used.

EXAMPLE 3Pharmacokinetics of GLP-1(7-36)amide and GLP-1(7-37) after nasal administration in phospholipid vehicle formulation.

The study was carried out in fasted New Zealand White rabbits (male, weighing $2,7 \pm 0,2$ kg) having an intravenous line in one ear for withdrawal of blood samples.

The following formulations were used in the study:

Formulation 1: GLP-1(7-36)amide (500 μ g) was dissolved in 1 ml of the phospholipid vehicle. 100 μ l of this formulation was applied in one nostril in each of eight rabbits.

Formulation 2: GLP-1(7-37) (600 μ g) was dissolved in 1 ml of the phospholipid vehicle. 100 μ l of this liquid formulation was applied in nostril in each of eight rabbits.

The formulations were administered using an Eppendorf multi-pipette.

Table 3 shows the observed plasma concentrations of GLP-1(7-36)amide and GLP-1(7-37) respectively in picomoles (pM) as a function of time after administration of the formulations.

Tabl 3

Time	Formulation No. 1		Formulation No. 2	
	pM, Mean	SEM (n=8)	pM, Mean	SEM (n=8)
0 min	78	4	68	9
2 min	101	6	118	7
4 min	155	28	305	42
6 min	292	62	640	116
8 min	377	63	835	114
10 min	372	58	899	107
12 min	386	46	907	125
14 min	383	42	838	116
16 min	363	37	826	111
18 min	324	35	755	96
20 min	294	26	698	98
25 min	261	29	505	73
30 min	231	18	333	41
45 min	157	8	175	22
60 min	130	5	146	17

These data further support the finding that the phospholipid formulations provide a protracted delivery of the peptides. As demonstrated in Example 2, the plasma concentrations exhibit a plateau (with plasma concentration increments > 50 % of the maximal increment) between 6 and 25 minutes after the delivery.

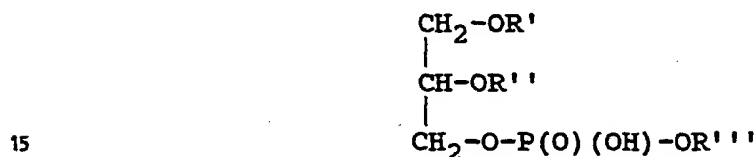
CLAIMS

1. A medicament for intranasal administration of a peptide fragment of formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-
 5 Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-
 Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X

(I)

wherein X is NH_2 or Gly-OH, or analogues or functional derivatives thereof, characterized in that it further comprises at least one phospholipid of the general formula II:



(II)

wherein R' and R'' are the same or different each representing hydrogen, alkyl, alkenyl, alkanoyl, alkenoyl, alka-
 20 dienoyl, alkatrienoyl or alkatetraenoyl containing not more than 14 carbon atoms in each group, with the proviso that R' and R'' are not hydrogen at the same time, and R''' is 2-(trimethylammonio)ethyl, 2-aminoethyl or 2,3-dihydroxypropyl.

2. A medicament according to Claim 1, characterized
 25 in that X in formula I is NH_2 .

3. A medicament according to Claim 1, characterized in that X in formula I is Gly-OH.

4. A medicament according to any one of the preceding claims, characterized in that R''' in formula II is 2-(trimethylammonio)ethyl.
5. A medicament according to any one of the preceding claims, characterized in that R' in formula II is alkyl or alkanoyl having from 4 to 12 carbon atoms, preferably alkanoyl.
6. A medicament according to Claim 5, characterized in that R' in formula II is decanoyl.
7. A medicament according to any one of the claims 1 to 4, characterized in that R' is hydrogen, with the proviso that R'' is different from hydrogen.
8. A medicament according to any one of the preceding claims, characterized in that R'' in formula II is alkyl or alkanoyl having from 4 to 12 carbon atoms, preferably alkanoyl.
9. A medicament according to claim 7, characterized in that R'' in formula II is decanoyl.
10. A medicament according to any one of the claims 1 to 6, characterized in that R'' is hydrogen, with the proviso that R' is different from hydrogen.
11. A medicament as described in anyone of the claims 1 to 10, characterized in that it comprises a solid diluent.
12. A medicament as described in Claim 11, characterized in that the content of the peptide of formula I in Claim 1 or analogues or functional derivatives thereof is in the range of from 0.01 to 75 % (W/W), preferably from 0.1 to 50 % (W/W), more preferred from 0.5 to 25 % (W/W).

13. A medicament as described in anyone of the claims 11 and 12, characterized in that the total content of phospholipids of formula II in Claim 1 is in the range of from 10 to 99 % (W/W), preferably from 10 to 80 % (W/W),
5 more preferred from 25 to 60 % (W/W).

14. A medicament as described in anyone of the claims 1 to 10, characterized in that it comprises a liquid diluent.

15. A medicament as described in Claim 14, characterized in that the content of the peptide of formula I in Claim 1 or analogues or functional derivatives thereof is in the range of from 0.0005 to 10 % (W/W), preferably from 0.001 to 5 % (W/W), more preferred from 0.01 to 5 % (W/W).

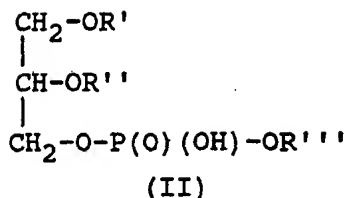
16. A medicament as described in anyone of the claims 14 or 15, characterized in that the total content of phospholipids of formula II in Claim 1 is in the range of from 0.01 to 20 % (W/W), preferably from 0.05 to 10 % (W/W), more preferred from 0.1 to 5 % (W/W).

17. A method of making a medicament for intranasal
20 administration of a peptide fragment of formula I:

His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-
Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-
Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X

(I)

25 wherein X is NH₂ or Gly-OH, and analogues and functional derivatives thereof and further comprising at least one phospholipid of the general formula II:



wherein R' and R'' are the same or different each representing hydrogen, alkyl, alkenyl, alkanoyl, alkenoyl, alka-
 dienoyl, alkatrienoyl or alkatetraenoyl containing not more
 10 than 14 carbon atoms in each group, with the proviso that R'
 and R'' are not hydrogen at the same time, and R''' is 2-
 (trimethylammonio)ethyl, 2-aminoethyl or 2,3-dihydroxy-
 propyl, which method comprises mixing the required amounts
 of the peptide fragment of formula I and at least one phos-
 15 pholipid of formula II, optionally in a solid or in a
 liquid diluent, and optionally further adding pH buffering
 agents, osmotic pressure controlling agents, preservatives
 or other ancillary agents.

184. A medicament as described in anyone of the
 20 claims 1 to 16 when used as an insulinotropic agent in the
 treatment of diabetes.

19. Use of the medicament of anyone of the claims 1
 to 16 or as prepared according to Claim 17 in a dosage dis-
 pensing device adapted for intranasal administration.

25 20. Any novel feature or combination of features as
 herein described.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 93/00098

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 37/28, A61K 47/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BIOSIS, EMBASE, MEDLINE, WPI, CHEMICAL ABSTRACTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A1, 911457 (BUCKLEY DOUGLAS I. ET AL), 8 August 1991 (08.08.91), see page 28 lines 24-28 --	1-20
X	WO, A1, 8804556 (NOVO INDUSTRI A/S), 30 June 1988 (30.06.88) --	1-20
A	WO, A1, 9009385 (THE LIPOSOME COMPANY, INC.), 23 August 1990 (23.08.90) --	1-20
A	WO, A1, 9102545 (DANBIOSYST UK LIMITED), 7 March 1991 (07.03.91) -----	1-20

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT
Information on patent family members

28/05/93

International application No.

PCT/DK 93/00098

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WO-A1-	911457	08/08/91	NONE		
WO-A1-	8804556	30/06/88	AU-B-	606121	31/01/91
			AU-A-	1085888	15/07/88
			DE-A-	3780925	10/09/92
			EP-A,B-	0272097	22/06/88
			SE-T3-	0272097	
			JP-T-	1501550	01/06/89
			US-A-	5179079	12/01/93
			ZA-A-	8709284	16/06/88
WO-A1-	9009385	23/08/90	AU-A-	5173690	05/09/90
			EP-A-	0458894	04/12/91
WO-A1-	9102545	07/03/91	EP-A-	0487562	03/06/92